REMARKS

Claims 1-3, 5-13, 15-17, 19-21 & 24-30, 44-47 are currently pending in the application. Only claims 1, 11, 15, 19, are in independent form.

The Office Action requests that applicant clarify the status of the case with respect to the priority document PCT/GB98/00374. It is stated that the oath refers to the invention with a different title than that of the present application. Additionally, the Office Action states that the oath or declaration is defective. Applicants have previously submitted a substituted declaration on December 28, 1999 to clarify these inaccuracies.

The Office Action objects to the use of "Bio-Dot" and Tween" stating that these are trademarks and as such must be accompanied by generic terminology. However, the Tween formulation is considered to be a generic formulation and as such does not necessitate further information as it is not a trademark. The term "Bio-Dot" as such has been capitalized wherever mentioned in the specification.

Claims 1-43 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Office Action states that claims 1-14 recite methods and kits for monitoring liquids for the presence of disease-modified or associated proteins. The Office Action states that while Applicant recites the conventional assays in sufficient detail for one of skill in the art to perform them in general, Applicant fails to describe the claimed invention in sufficient detail as to enable one of skill in the art to make and use the invention. However, Applicant has limited the claims to claim only calcium phosphate as the non-buoyant particulate material thus clarifying that calcium phosphate is a preferred material which can be utilized in the present invention. Further, there is specifically set forth in the examples the exact solutions to utilize for the methods and kit of the present invention. As such, there is sufficient support in the specification to practice the claimed invention, therefore the methods of the claimed invention would not require undue experimentation by one of skill in the art to make and/or use the claimed invention.

The Office Action states that claims 15-18 recite methods for concentrating disease modified or associated proteins from a sample of liquid. Specifically, the Office Action states that step (k) of claim 15 recites "collecting supernatant containing the disease-modified or associated proteins" after centrifugation. However, this step has been amended to state "collecting said calcium phosphate" corresponding to the present description

on page 9, line 9 which more specifically states what is included in step (k) of claim 15.

The Office Action states that claims 19-30 recite methods of monitoring a liquid for the presence of disease-modified or associated proteins, protein fragments, viruses and virus fragments utilizing a solid filter medium having free ionic valencies. The Office Action states that Applicant fails to describe either the source of the filter material nor the means for its manufacture. Additionally, the Office Action states that the art does not teach the existence of a fiber sheet with a weave interval of 1 to 100 microns. However, it is well known in the art that filter material can be made to any number of specific dimensions. For example, Whatman plc makes a number of different filter papers which can function for any number of different purposes, and further can be made to any specific dimensions as required. Therefore, there is sufficient disclosure and knowledge in the art regarding the filter material recited in the claims. Accordingly, reconsideration of the rejection is respectfully requested.

Claims 31-43 recite methods of monitoring a liquid for the presence of disease-modified or associated proteins, protein fragments, viruses and virus fragments utilizing a solid, non-buoyant particulate matter having free ionic valencies. Again, the Office Action states that combining the use of particulate matter and the solid filter media into a single method would not allow one of skill in the art to make and use the claimed invention since

the manufacture and use of each of the aforementioned components are not enabled, as discussed previously. As set forth above, there is sufficient support in both the prior art and the present application for the amended claims. Particularly, the claims have been amended to recite a granular calcium phosphate which is sufficiently supported in the specification. Further, there is sufficient knowledge in the art for the use of the filter material of the claimed methods. Accordingly, reconsideration of the rejection is respectfully requested.

Claims 3, 13, 17, 21 and 33 specifically recite the use of the aforementioned methods to monitor urine for the presence of disease-modified or associated proteins, protein fragments, viruses, or virus fragments. The Office Action states that Applicant fails to describe what particular proteins or viruses would be present in the urine or what specific reagents would be needed to detect said proteins and viruses or how to associate them with particular diseases. However, the specification does disclose several proteins or viruses or virus fragments present in urine. For example, on Page 4, line 20, there is disclosed that protein "nemavirus" is associated with KJD disease and is present in urine. Further the protein core of the nemavirus comprises the protease-resistant protein (PrP) which is set forth on Page 3, line 13. Further, the use of an antibody to PrP in ELISA according to the present invention is disclosed on Page 11, line 11. Yet another example of a disease-modified protein which is present in urine is found in patients with Alzheimer's disease. In Alzheimer's disease segments

of the amyloid β-precursor protein are found in the urine of patients with the disease as disclosed on Page 6, line 13 of the specification. While the specification does not specifically mention the presence of amyloid β-precursor protein in the urine of patients with Alzheimer's disease, it is implied from the following sentence which discloses that "in contrast, the urine of patients testing negative for Alzheimer's disease will not contain segments of the amyloid β-precursor protein." Further examples of viruses that may be excreted in urine are cytomegalovirus, papillomavirus or the aids virus, all of which are set forth on Page 7, line 3, and various other viruses associated with certain cancers, growths, etc. (See Page 7, line 17). Accordingly, reconsideration of the rejection is respectfully requested.

The Office Action states that claim 9 recites the amplification of concentrated proteins by PCR and subsequent monitoring by restriction length method. The Office Action states that the specification does not teach how to perform PCR using proteins and hence is not enabled. Accordingly, the claim 9 and 29 has been amended to claim "amplifying DNA associated with said aggregated protein material" to specifically teach how to perform PCR using these proteins. Reconsideration of the rejection is respectfully requested.

The Office Action states that claim 10 recites the use of concentrated proteins in a hybridization reaction and subsequent monitoring

using Western blotting. In order to further prosecution, claim 10 and 30 has been canceled.

Claims 1, 4, 11, 14, 15, 18, 22, 23, 31 and 34-36 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards the invention.

The Office Action states that claims 1, 11, 15 and 31 recite the term "solid, non-buoyant particulate material having free ionic valencies" which is vague and indefinite. The claims have been amended to more specifically recite the claimed compound thus eliminating any vagueness or indefiniteness. Reconsideration of the rejection is respectfully requested.

Claims 4, 14, 18 and 34 recite the term "calcium phosphate in granular form" which the Office Action states is vague and indefinite. In order to further prosecution, these claims have been canceled without prejudice.

Claims 22 and 35 recite the term "comprises a gauze fiber material" which is vague and indefinite. Accordingly, in order to further prosecution, claims 22 and 35 have been canceled without prejudice.

Claims 23 and 36 recite the term "comprises a cotton fiber material" which is vague and indefinite according to the Office Action. Claims 23 and 36 have been canceled without prejudice.

Claims 1-21, 24-33 and 37-43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Schenk et al patent in view of the Alaska et al patent and the Chu et al patent. Reconsideration of the rejection is respectfully requested.

Specifically the Office Action states that independent claims 1 and 15 recite methods for monitoring/concentrating liquids for the presence of disease-modified or associated proteins by concentrating the proteins by contacting a solid non-buoyant particulate material having free ionic valencies and subsequently monitoring the concentrated protein via a myriad of conventional assays. The Office Action states that the Schenk et al patent discloses the monitoring of Alzheimer's disease-associated protein, beta-amyloid protein, in biological fluids as means of predicting Alzheimer's disease. The Office Action states that the Schenk et al patent further discloses that β-amyloid protein is present in very low concentrations in biological fluids such as blood, cerebrospinal fluid, urine and peritoneal fluid. It is true that the Schenk et al patent discloses the monitoring of Alzheimer's disease-associated protein, β-amyloid peptide and biological fluids using detection techniques such as ELISA, Western blotting, radioimmunoassay and the like. While the Schenk et al patent discloses the use of affinity

purification to concentrate the protein, it does not disclose the use of a solid non-buoyant particulate matter or a solid filter medium for such concentration. These methods are utilized in the presently pending independent claims.

The Office Action further states that the Alaska et al patent discloses the use of hydroxyapatite, which is a solid non-buoyant particulate material, for the binding of proteins in biological fluids. This use is not at all similar to the method in the presently pending independent claims. The Office Action states that it would have been obvious for one of skill in the art to use like compounds in order to optimize the system of the Schenk et al patent and one would have a high expectation of success, since, hydroxyapatite and granular calcium phosphate are similar compounds. Therefore, the Office Action concludes that it would have been obvious to one of skill in the art to use the concentration method disclosed in the Alaska et al patent and the monitoring methods disclosed by the Schenk et al, because the combination would yield a higher concentration of the Alzheimer's disease-associated protein which could then be used in more cost effective detection assays.

Although the Office Action states that hydroxyapatite is a solid non-buoyant particulate material, the disadvantages of using the hydroxyapatite for the present invention are disclosed in the specification of the present application. Calcium phosphate is advantageous in the present invention because it overcomes these difficulties. While using calcium phosphate is an

advantage for the present invention, it has no particular significance in the Alaska et al patent. Also, the Alaska et al method discloses a method which is much more complicated than the method of the present invention which can simply involve centrifugation. Thus, it would not have been obvious to use the compounds of the Alaska et al patent with monitoring methods of the Schenk et al patent. Further, even if one did combine these two prior art patents, one would still not arrive at the method of the present invention.

Additionally, when read more specifically, the Alaska et al patent discloses the use of hydroxyapatite to remove protein contaminants from a solution thereby leaving the thrombopoietin substantially unbound. This is in contradistinction with the present invention which utilizes granular calcium phosphate to concentrate the disease-modified or associated proteins from a sample so that they can be monitored. In order words, the Alaska et al patent uses the hydroxyapatite to remove protein contaminants from a sample thus leaving what they are trying to analyze which contrasts with the presently pending independent claims which instead remove the disease-modified or associated protein utilizing the calcium phosphate. Since the combination of the Alaska et al patent and the Schenk et al patent would not disclose the methods of the presently pending independent claims, reconsideration of the rejection is respectfully requested.

The Office Action states that claims 19-21 and 24-30 recite methods for monitoring a liquid for the presence of biological material by

using a solid filter medium having free ionic valencies and subsequently testing bound material by electron microscopy or other testing methods. The Office Action states that the Chu et al patent discloses the use of a microporous membrane for the removal/concentration of proteins and microorganisms and that such use is well known in the art. Additionally, the Office Action states the Chu et al patent discloses the use of anionic microporous membrane for the purification of liquids. The Chu et al patent does not disclose the use of the microporous membranes for the concentration of the protein or viruses for monitoring disease associated proteins but the Office Action states it would have been obvious for one of skill in the art to use the concentration methods disclosed by Chu et al with the monitoring methods disclosed by the Schenk et al patent because this combination would yield a higher concentration of the proteins which could then be used in a more cost effective detection assay. The Chu et al patent discloses the use of an anionically charged microporous filter membrane for the filtration of fluids. This is different from the present invention where instead the emphasis is placed upon using a solid medium to concentrate disease modified or associated proteins to enable the proteins to be monitored. There is no disclosure in the Chu et al patent for the use of membranes for protein or virus concentration, but instead the Chu et al patent merely use these membranes for the filtration of fluids. Therefore, even combining the Chu et al membrane with the Schenk et al method would not yield the method of the presently pending independent claims because there is no disclosure of a protein concentration step similar to that of the presently

pending independent claims. Since the combination of the Chu et al patent and the Schenk et al patent do not disclose the methods of the presently pending independent claims, reconsideration of the rejection is respectfully requested.

Claims 31-34 and 37-43, according to the present Office Action, are anticipated by the combination of the Alaska et al patent with the Chu et al patent and the Schenk et al patent. The Office Action concludes that it would have been obvious for one of skill in the art to combine the use of a solid, non-buoyant particulate matter having free ionic valencies and the anionic microporous membrane of the Chu et al patent with the monitoring methods of the Schenk et al patent. However, there is no indication any of these patents for the combination of these methods. Further, even if one were to suggest the combination of these three patents, one would not yield the method of the presently pending independent claims. Because as set forth previously, the Alaska et al patent does not disclose a similar method to that of the presently pending independent claims. Further, the Chu et al membrane is substantially different and has not been disclosed to perform in the same manner as the membrane of the presently pending independent claims. Accordingly, the combination of all these three patents would not result in the methods of the presently pending independent claims, and reconsideration of the rejection is respectfully requested.

The Office Action states that claims 11-14 recite an ELISA kit and a solid, non-buoyant particulate matter added for binding proteins to be tested. For the reasons described above, the Office Action states that the use of granular calcium would have been obvious in light of the prior art. Additionally, bundling the materials to use together in the form of a kit would also be obvious to one of skill in the art for it would result in greater ease of use and would be more economical. However, as set forth above, neither the method of the presently pending independent claims nor the kit are obvious in light of the prior art in that the methods and the kit of the presently pending independent claims provide different materials from those disclosed in the prior art and function in completely different ways than that of the prior art. Since the combination of the prior art does not disclose the kit of the presently pending independent claims, reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on April 20, 2000.

Marie M. DeWitt